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UNIQUE EFFECTS OF INFECTIOUS OR INFLAMMATORY STRESS ON FAT META--ETC(U)
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Infectious or inflammatory stress in the rat causes very typical functional and metabolic alterations. Among the most typical are elevation in body temperature, plasma copper, insulin, and glucagon and depression in the concentration of plasma ketones, free fatty acids and zinc. These changes occur only with infectious or inflammatory stress and not with noninflammatory stresses such as femoral fracture, screen restraint or exercise. It appears that the depression in plasma ketone bodies during infection or inflammation		

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is closely related to the rise in plasma insulin. During infection imposed on experimentally induced diabetes, inhibition of plasma ketones is not apparent. In a similar fashion, infection in hypophysectomized rats causes no elevation in plasma insulin and no depression in plasma ketones. Discussion concerning the implications of these observations in the rat and primate is included.

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Unique Effects of Infectious or Inflammatory stress on Fat Metabolism in
Rats,

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The Fort Detrick facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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Abstract: Infectious or inflammatory stress in the rat causes very typical functional and metabolic alterations. Among the most typical are elevation in body temperature, plasma copper, insulin, and glucagon and depression in the concentrations of plasma ketones, free fatty acids and zinc. These changes occur only with infections or inflammatory stress and not with noninflammatory stresses such as femoral fracture, screen restraint or exercise. It appears that the depression in plasma ketone bodies during infection or inflammation is closely related to the rise in plasma insulin. During infection imposed on experimentally induced diabetes, inhibition of plasma ketones is not apparent. In a similar fashion, infection in hypophysectomized rats causes no elevation in plasma insulin and no depression in plasma ketones. Discussion concerning the implications of these observations in the rat and primate is included.

The purpose of this review is to summarize metabolic alterations, specifically those relating to lipid metabolism, which occur when rats are stressed under controlled conditions with either an infectious or inflammatory stress. When rats are subjected experimentally to an inflammatory stress there are common metabolic aberrations which ultimately lead to a significant loss in body nitrogen. These metabolic responses generally emerge in a consistent pattern, whether the inflammatory process is initiated by an infectious microorganism or by a sterile irritant.

Many of the inflammation-related metabolic alterations observed in fasted rats differ from the typical metabolic changes seen in fasted control rats and, therefore, are of interest to those involved with the study of metabolic events during disease. Data from the rat cannot, of course, be transferred directly to metabolic events occurring in the septic human. However, the possible relationships between results discussed in the rat and those observed in the septic human patient will be discussed later.

Of all the measured metabolic differences between infected and uninfected fasting rats, the specific parameters reported here were chosen because they reflect characteristic and consistent differences attributable to the presence of infection. These parameters include rectal temperature, and plasma concentrations of zinc, ketone bodies, free fatty acids, copper, insulin and glucagon. All of these components can be defined by rather narrow limits in the normal fed rat. Plasma ketone bodies (β -hydroxybutyric acid and acetoacetic acid) are present in concentrations ranging from 0.5-1.0 $\mu\text{mol/ml}$, free fatty acids from 250-750 $\mu\text{Eq/L}$, insulin ranges from 15-30 $\mu\text{U/ml}$, glucagon from 250-500 pg/ml and

zinc and copper from 120-150 $\mu\text{g/ml}$. In general, fasting for 24 or 48 hrs causes a lowering of body temperature and marked increases in both plasma ketone bodies and free fatty acids. Plasma insulin (I) decreases during fasting, but there is little or no change in plasma glucagon (G); the combination of these changes depresses the I/G ratio. Fasting causes only a slight decrease in plasma zinc concentration and essentially no change in plasma copper. In the reviewed studies, both stressed and control rats were fasted to accomodate the anorexia which normally accompanies an experimentally induced acute infection or inflammatory process.

A. Stress

Stress can be defined as the sum of all nonspecific biological phenomena elicited by adverse external influences. These may include cellular damage and may be localized or systemic. Stress may be characterized further as inflammatory or noninflammatory. For the purposes of this review, inflammatory stresses are characterized as those which may result in fever, anorexia and cell damage or death. As examples of inflammatory stress we have chosen two bacterial infections, gram-positive, Streptococcus pneumoniae and gram-negative, Francisella tularensis; one viral infection, Venezuelan equine encephalomyelitis; the administration of Eschericia coli endotoxin; and the induction of a sterile turpentine abscess. In all studies appropriate controls were utilized. When experimental rats were given bacterial or viral pathogens, control groups received equal numbers of heat-killed organisms. Control groups for rats receiving endotoxin or turpentine received sterile normal saline. As examples of noninflammatory stress in rats, screen restraint,¹ a noninvasive femoral fracture,² and swimming exercise were chosen.³

Data on noninflammatory stresses have been included to illustrate clearly that the important metabolic consequences of infection are not necessarily associated with trauma, which can be noninflammatory. Swimming exercise has been included as a noninflammatory stress, although, clearly, it represents a totally different type of stress than screen restraint or femoral fracture. Severe exercise may be considered as a noninflammatory stress because, normally, it is not associated with the localized cellular death observed during the inflammatory process.

B. Effect of inflammatory and noninflammatory stress on body temperature, plasma zinc, and plasma copper.

All infectious and noninfectious inflammatory processes included in these studies caused a significant increase in rectal temperature within 24 hrs after initiating the stress (Fig. 1). In general, depending on the severity of the stress, increases in body temperature were apparent as early as 6 hrs (endotoxin) or delayed until 24 hrs (viral infection). Rats subjected to the noninflammatory stresses of screen restraint or femoral fracture did not become febrile (data not shown), and during a 10-hour swim in thermoneutral water (33-35°C), body temperature dropped due to the high thermal conductivity of the water.

As described by Pekarek, Beisel, and their co-workers,⁴⁻⁹ one of the earliest indications of inflammatory stress is the depression in plasma zinc. The effect of infectious or inflammatory stress on plasma zinc and plasma copper in rats is shown in Figure 2. The depression in plasma zinc is accompanied by an increase in liver zinc.¹⁰ Most of the excess hepatic zinc is sequestered in the liver by an acutely induced zinc binding metallothionein. In like fashion, the elevation of plasma copper is associated with increased hepatic synthesis and release into the plasma of copper-binding ceruloplasmin. Rats subjected to a variety

of noninflammatory stresses demonstrated no change in plasma zinc or copper. Although a depression in plasma zinc and a rise in plasma copper are excellent indices of inflammatory stress, it is not clear as to how, or if, these events might benefit the host.

C. Effect of inflammatory and noninflammatory stress on plasma ketones, free fatty acids, and albumin.

Inflammatory processes caused a severe inhibition of the ketonemia typically associated with fasting (Fig. 3) and a depression of concentration of plasma free fatty acids¹¹⁻¹³ (Fig. 4). In contrast, a noninflammatory stress such as a femoral fracture caused no decrease in plasma ketone concentration of fasted rats² (Fig. 3). The stress of prolonged (3 hrs) swimming exercise caused an increase in plasma ketone bodies and free fatty acids in fasted rats (Fig. 5); however, the direction of change due to fasting as similar in both sedentary and swimming rats. There is no indication that the exercise-stress disrupted the mechanism which caused the infection-induced fasting ketonemia.¹⁴

Decreased ketonemia during inflammatory stress in fasting rats is accompanied by significant depressions in ketone body concentrations in brain and liver (Fig. 6). Moreover, as shown by Wannemacher et al¹⁵ and in Figure 7, when livers from infected rats were perfused with long-chain fatty acids, the ability of the liver to produce ketone bodies was diminished, even if the free fatty acid concentration in the perfusate was maintained at or above that found in normal plasma.

For many years it has been assumed that the brain utilizes glucose almost exclusively and adapts to the use of ketone bodies only after severe fasting.¹⁶ The use of ketones by the brain has been shown by Owen et al.¹⁷ Recent work by Hawkins and Biebuyek¹⁸ suggests that

ketones are selectively used by individual brain regions which require no period of adaptation.

The decrease in plasma free fatty acid concentration during infection is probably related to the concomitant decrease in plasma albumin, its carrier protein. This can be deduced from data which show that the free fatty acid to albumin ratio remains relatively constant when plasma from fasted-infected rats is compared to fasted controls, as shown in Figure 8.¹⁵ When a noninflammatory stress such as an aseptic femoral fracture or screen restraint, was imposed on rats, there was a decrease in plasma free fatty acids (Fig. 9).² In contrast, however, the stress of swimming elevated free fatty acids (Fig. 5).¹⁴

The data presented in Figure 7 suggest that the decrease in ketone body production in the livers of infected rats is most probably due to a change in the manner in which the liver handles the flux of long-chain free fatty acids. Data obtained by Pace *et al*¹⁹ indicated that in livers from infected rats there was a shift toward the synthesis of triglycerides rather than production of ketone bodies.

D. Effect of inflammatory and noninflammatory stress on the endocrine system.

Several investigations²⁰⁻²⁴ have noted a rise in plasma insulin during infection. Figure 10 shows the effect of a variety of stresses on plasma insulin concentration. Inflammatory stresses cause insulin values in the fasted rat to increase to, or near, the concentration seen in fed rats. In studies of noninflammatory stress, the insulin concentration remains as low as in normal fasted rats. There seems to be a close association between high plasma insulin values and low ketone bodies. If, for example, an infectious stress is imposed upon a fasted insulopenic rat

(Fig. 11), depression of plasma ketones does not occur. Moreover, Foster et al²⁵ demonstrated that the administration of insulin rapidly caused a reversal of fasting ketosis. The data presented in Figure 12 show that the iv injection of 1 unit of insulin into a rat fasted for 24 hrs caused a rapid drop, within 3 min, in the concentration of ketone bodies. The depression was transitory and 15 min after insulin administration, recovery began. By 1 hr postinsulin administration, plasma ketone body concentration had exceeded the fasted value.

Infectious stress caused not only an increase in plasma insulin but also a dramatic increase in plasma glucagon (Fig. 13). The magnitude of the glucagon increase exceeded that of insulin, so that there was a marked reduction in the I/G ratio (Fig. 14). During prolonged swimming, plasma insulin values changed little from those of fasted unexercised rat. If, however, noninfected and infected rats were compared, swimming exercise during sepsis diminished the infection-induced increase in plasma insulin. Plasma glucagon, however, increased due to exercise and this increase was not diminished during superimposed infection¹⁴ (Fig. 15). When a single injection of glucagon was given to a fed rat (Fig. 16) a rapid rise in the concentration of plasma glucose, free fatty acids and ketones could be detected in minutes. Following the glucagon-induced rise in these plasma parameters, there was a rapid rise in plasma insulin, which was followed immediately by a drop in ketones, free fatty acids and glucose. Data such as these tend to demonstrate that although glucagon is ketogenic, its effect is rapidly overwhelmed and reversed by insulin. Thus, the altered I/G ratio in infection caused both by an increased insulin and a much larger increase in glucagon would tend to support the theory of the predominant role for insulin in the impaired ketogenesis seen in the rat during infection.

When thyroidectomized or adrenalectomized rats are infected, the ketone response is comparable to that seen in the infected intact rat. Data such as these suggest that the thyroid gland, the adrenal cortex and the adrenal medulla are not involved in the infection-induced diminished plasma ketone body concentration (Fig. 17). When, however, hypophysectomized rats were inoculated with S. pneumoniae and fasted, there was no inhibition of the fasting-induced concentration of plasma — ketone bodies¹⁸ or free fatty acids (Fig. 19). Additionally, the concentration of plasma insulin in the fasted and the fasted infected hypophysectomized rat was so low that often it was below the limits of the assay.²⁴ This observation supports further the reciprocal relationship of insulin values and ketone response in infected rats.

E. The effect of inflammatory stress on malonyl-CoA, carnitine derivatives, and mitochondrial oxidation of free fatty acids.

Pace et al¹⁹ showed that bacterial infections caused no change in the oxidation of palmitylcarnitine by rat liver mitochondria, suggesting that the process of β -oxidation, and the tricarboxylic acid cycle were not altered in infected rats. There were, however, alterations in carnitine derivatives as shown in Table I. Infection caused a marked increase in the concentration of short-chain acylcarnitines, especially acetylcarnitine, and a marked decrease in long-chain acylcarnitines.¹⁹ The total carnitine (free plus short-chain plus long-chain acylcarnitine) increased with infection when compared to the fasted uninfected control. Fasting and/or infection caused a significant decrease in the content of malonyl-CoA.

Moreover, there is a characteristic deposition of lipid droplets in the cytosol of livers from infected rats.¹⁹ These data, together

with the changes in the carnitine derivatives, suggest that inflammatory stress may cause a change in the metabolic pathways of hepatic cells, away from ketone formation, and toward fatty acid and triglyceride synthesis. If, indeed, this is so, this may represent a fatty acid futile cycle in that fatty acids mobilized from triglycerides in the adipose tissue end up as triglyceride droplets in liver cytosol.

F. Interpretation: The rat

The metabolic variations that result from an infectious stress in the rat are apparent in general noninfectious inflammatory stresses as well. The inflammatory stresses studied precipitate several important parametric variations, namely: fever, plasma zinc depression, inhibition of fasting ketosis, depression of plasma free fatty acids and elevation of plasma insulin, glucagon, and copper. These changes occur in different time sequences, depending on the severity and acuteness of the particular stress and, if low-dose inocula of bacteria are given, and the incubation period is lengthened, the changes simply occur later.

The changes in the metabolic parameters which have been discussed are so general that it is highly probable that in all the infectious and noninfectious inflammatory stresses studied common mechanisms are called into play. Pekarek and his colleagues²⁶ have demonstrated that an inflammatory stress caused the production of a factor they called leukocytic endogenous mediator (LEM). LEM isolated in crude form from leukocytes stimulated by glycogen granules in the peritoneal cavity of the rabbit have been demonstrated to cause many of the parametric variations caused by infectious stress.

It would be tempting to suggest that LEM might be the common factor. However, careful analysis of the data suggests that at least

two, and probably more, mechanisms are called into play. For example, although crude LEM injected into rats causes fever and depressed plasma zinc and ketones, it cannot be the sole responsible agent. Neufeld et al²⁴ have shown that when hypophysectomized rats are infected, only plasma zinc is depressed -- ketone body responses appear to be unaffected. A better approach is to postulate that the inflammatory stress sets into motion a number of responses; one causing elevated insulin and depressed ketones and involving the hypophysis and the pancreas; a second, involving depression of plasma zinc; a third, concerned with fever; and others such as acute-phase protein synthesis and neutrophil mobilization, not covered in this review.

The net result, in the rat, is that there is an altered ability of the rat to use fatty acids for fuel during infectious stress. Ketone production is severely inhibited and some fatty acids seem to be redeposited in liver cytosol as triglycerides.

G. Interpretation: Primates

While data from any animal and, in particular, the rat can be transferred to the human situation only with great care, there is some evidence that the effect of infectious stress described here may be common to the primate. In the rat as well as the human, fasting causes, after a suitable time period, a rise in plasma ketone bodies and, in both species, uncontrolled diabetes results in ketoacidosis. The exact conditions described in this review for the rat cannot be obtained for the human, since a human patient would not purposefully be deprived of nutritional support. However, it is not unreasonable to theorize that some similar train of events takes place.

Two of the most consistent observations from experiments with the rat stressed with infectious or noninfectious inflammatory stresses

were the rise in plasma insulin and glucagon. The rise in plasma glucagon was of a larger magnitude than the rise in insulin resulting in a decreased I/G ratio. Similar observations have been noted during infectious stress in primates. Shambaugh and Beisel²⁷ noted that experimentally induced tularemia in man resulted in a significant increase in plasma insulin. Rayfield et al²² found normal fasting baseline plasma values for both insulin and glucagon during sandfly fever in volunteers, but insulin responses to an infused glucose load were significantly increased. George et al²³ described elevated plasma insulin and glucagon concentrations in monkeys infected with S. pneumoniae. They noted, also, a decrease in the insulin/glucagon ratio and suggested that this decrease was indicative of a catabolic state. A similar proposal was made by Unger in 1972²⁸ and by Muller et al²⁹ in 1971.

In 1975, Sherwin, et al³⁰ demonstrated in both nonobese and obese human subjects that iv infusion of β -hydroxybutyrate during starvation resulted in hypoalaninemia and decreased protein catabolism. Also, in 1975, Bistrian and associates³¹ presented data which indicated that provision of carbohydrate-containing diets during stress was the cause of the higher than normal insulin concentrations resulting in the inhibition of lipolysis and ketogenesis. O'Donnel and associates in 1976,³² demonstrated in seriously ill, septic patients elevated insulin and markedly decreased values of ketone bodies in blood obtained from the femoral artery. They proposed that this combination resulted from enhanced gluconeogenesis together with an enhanced release of alanine and extensive proteolysis. They suggested that body cell mass could be conserved optimally in septic states by meeting an obligatory keto acid (derived from ketone bodies or branched-chain amino acids) energy requirement. This proposition is supported by data obtained by Sapier.³³

Other marked alterations in lipid metabolism during infection in primates have been noted by Kaufmann et al^{34, 35} and by Fiser et al.³⁶ Fiser et al showed that in the monkey, experimentally induced endotoxemia resulted in an increase in plasma triglycerides, which glucose administration could partially prevent; they noted a 40-50% decrease in plasma free fatty acid -- similarly shown for endotoxemia in the rat. Kaufman et al studied the role of Salmonella typhimurium endotoxin on lipid disposal mechanisms in rhesus monkeys. They demonstrated an increase in plasma free fatty acids shortly after administration of endotoxin, but this study was not carried beyond 8 hrs. Of greater significance was the marked hypertriglyceridemia which occurred 4-6 hrs after endotoxin administration. Administration of Intralipid markedly increased hypertriglyceridemia. Work by Siegel, Cerra and their associates^{37, 38} on a number of metabolic parameters in septic patients led to some interesting observations. In six septic patients who died, the metabolic state was characterized by an elevation of glucose, lactate, aromatic and branch-chain amino acids and glucagon, and by low values of ketone bodies.³⁷ In other studies,³⁸ however, these authors observed slight rises in ketone bodies, particularly acetoacetate, resulting in an altered cellular redox potential.

In a study with monkeys infected with S. pneumoniae, Wannemacher et al^{39, 40} demonstrated a marked drop in urinary β -hydroxybutyric acid which was closely correlated with negative nitrogen balance. This negative balance could be overcome by infusion with amino acids plus dextrose. In a detailed study in rats by Wannemacher et al,¹⁵ it was shown that sepsis caused a reduction in plasma free fatty acids; this could be explained as a consequence of an infection-induced decrease in

plasma albumin which is the fatty acid carrier. They also demonstrated that ketone body oxidation was not affected or reduced in peripheral tissues of the infected rat. According to the authors,¹⁹ the reduced rate of ketone body production was due to the tendency of the liver in the infected rat to shuttle fatty acids away from β -oxidation and ketogenesis towards triglyceride production and deposition in the liver cell -- the so-called futile cycle discussed earlier.

More recently Wannemacher et al⁴⁰ reported experiments in which butanediol and monacetoacetin were used as ketone precursors in septic monkeys. They found that butanediol was not only ineffective, but could be lethal. On the other hand, monoacetoacetin and a mixture of long-chain fatty acids and branched-chain amino acids were effective in preventing nitrogen wastage with few side effects.

All of these data tend to support the theory that the altered metabolic state reported for the rat during sepsis resembles closely the altered state seen in primates. Data such as these suggest that the proper mixture of nutrients can prevent or minimize the nitrogen wastage which usually accompanies sepsis. The major thrust of such nutritional support is in the direction of reducing gluconeogenesis from body protein and stimulating the use of ketone bodies or adequate precursors as high caloric substrates.

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TABLE I

EFFECT OF FASTING AND S. PNEUMONIAE INFECTION ON HEPATIC CARNITINE
AND MALONYL-CoA CONTENT AND RATE OF KETONE PRODUCTION BY LIVER MITOCHONDRIA *

Treatment	Liver wt. (gm)	Carnitine (nmol/gm)			Malonyl CoA (nmol/gm)	Mitochondria (nmol ketones/ min/mg Protein)
		Free	Short	Long		
Fed control	9.2 ± 0.9	155 ± 11	82 ± 13	77 ± 14	13.5 ± 3.10	2.3 ± 0.2
Fasted and killed-bacteria control						
24 hr	6.3 ± 0.1 [†]	237 ± 11 [†]	71 ± 12	88 ± 8	4.96 ± 1.62	2.8 ± 0.4
48 hr	5.8 ± 0.3 [†]	240 ± 19 [†]	70 ± 14	85 ± 13	4.80 ± 0.89 [†]	5.0 ± 0.7
Fasted and live bacteria						
24 hr	6.5 ± 0.4 [†]	200 ± 10	49 ± 8	45 ± 1 [‡]	3.29 ± 0.83 [†]	3.9 ± 0.6
48 hr	7.0 ± 0.3 [‡]	225 ± 16 [†]	129 ± 15 [‡]	54 ± 6 [‡]	3.25 ± 0.65 [†]	3.6 ± 0.8

* Values are mean ± SEM

[†] Significantly different from fed controls (p < 0.01).

[‡] Significantly different from fasted controls (p < 0.01).

FIGURE LEGENDS

Fig. 1: Effect of inflammatory stress on body temperature. All rats were fasted for 24 hrs and then infected or inoculated.

Fig. 2: Effect of inflammatory stress on plasma zinc and plasma copper. (□) Fed, (▨) Fasted, (■) Fasted and infected with 10^4 cells of S. pneumoniae/rat: zinc and copper were measured 24 hrs after infection.

Fig. 3: Effect of inflammatory and noninflammatory stress on plasma ketone body concentration. Ketone bodies were measured 48 hrs after imposition of the stress.

Fig. 4: Effect of inflammatory stress on plasma free fatty acids in the 48-hr fasted rat.

Fig. 5: Influence of a 48-hr S. pneumoniae infection (10^2 /rat) and 2-hr swim on plasma ketones and free fatty acids in the rat. (□) Sedentary fasted, (▨) Sedentary-fasted-infected, (▩) Exercise fasted, (■) Exercise-fasted-infected.

Fig. 6: Effect of S. pneumoniae infection on ketone body concentration in the rat brain and liver. (●) 10^4 S. pneumoniae, sc, (○) 10^4 heat-killed S pneumoniae, sc.

Fig. 7: Effect of infection on ketone formation in perfused livers.

Fig. 8: Effect of fasting and infection on the free fatty acid/albumin ratio in the plasma of rats.

Fig. 9: Effect of noninflammatory stress on plasma free fatty acids.

(○) controls, (□) Femoral fracture, (●) Screen restraint.

Fig. 10: Effect of inflammatory and infectious stress on plasma insulin.

Values are at the time of maximum insulin elevation.

Fig. 11: Effect of infection on plasma ketones in diabetic rats. (○)

Fed rats and rats which received no insulin after injection of heat-killed organism. (●) Fasted rats infected with S. pneumoniae which received no

insulin. (□) Fasted-control rats which received 2 U insulin. (■)

Fasted-infected rats which received 2 U insulin.

Fig. 12: Effect of insulin on the ketosis of fasting.

Fig. 13: Effect of infection (10^4 S. pneumoniae) on plasma glucagon. (●)

10^4 viable S. pneumoniae, sc, (○) 10^4 heat-killed S. pneumoniae, sc.

Fig. 14: Effect of infection on the molar I/G ratio.

Fig. 15: The effect of exercise on plasma insulin and glucagon in infected

rats. (□) Sedentary-fasted, (▨) Exercised-fasted, (▩) Sedentary-
fasted-infected, (■) Exercised-fasted-infected.

Fig. 16: Effect of a bolus of glucagon on plasma glucagon, insulin,

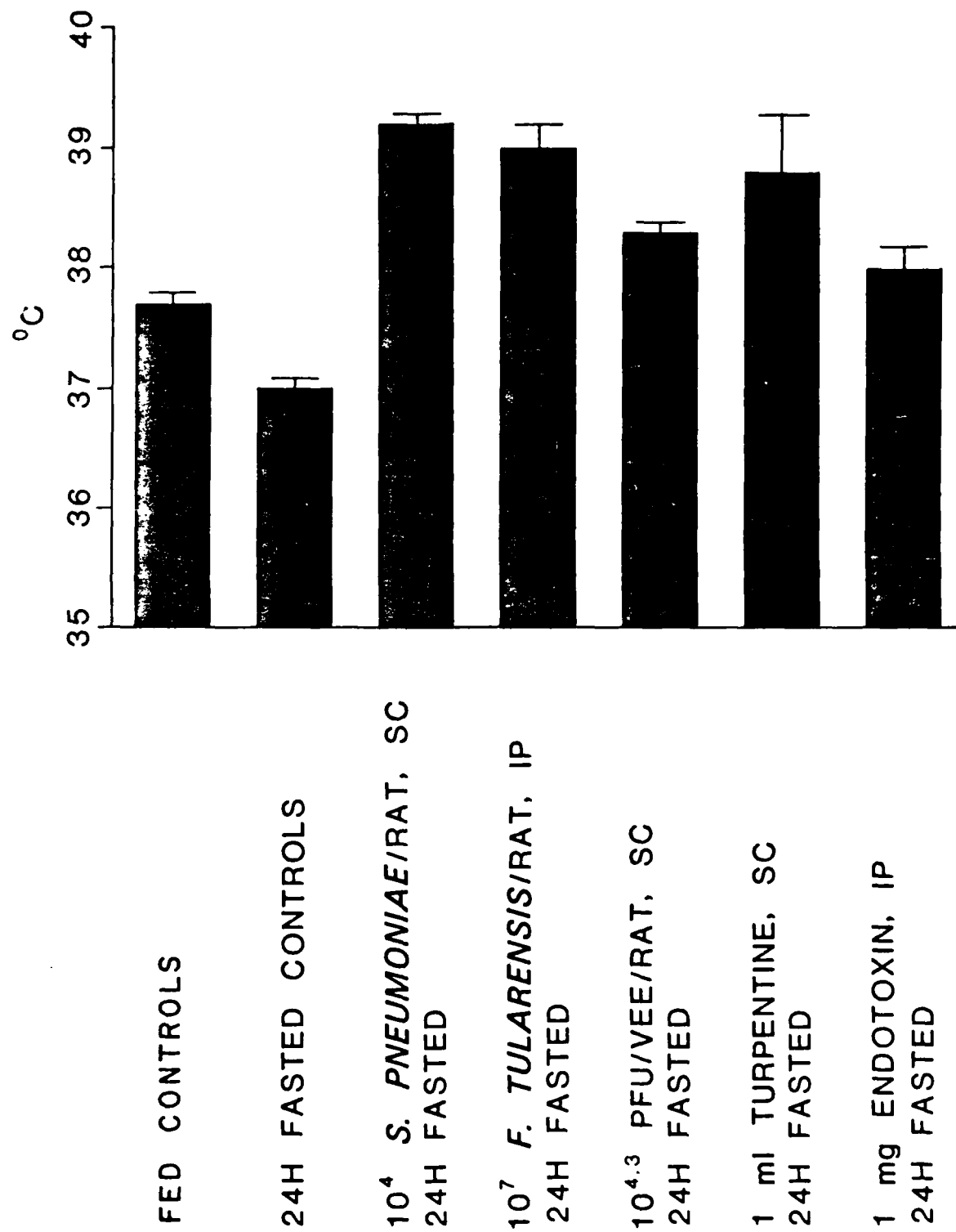
ketone bodies, free fatty acids and glucose.

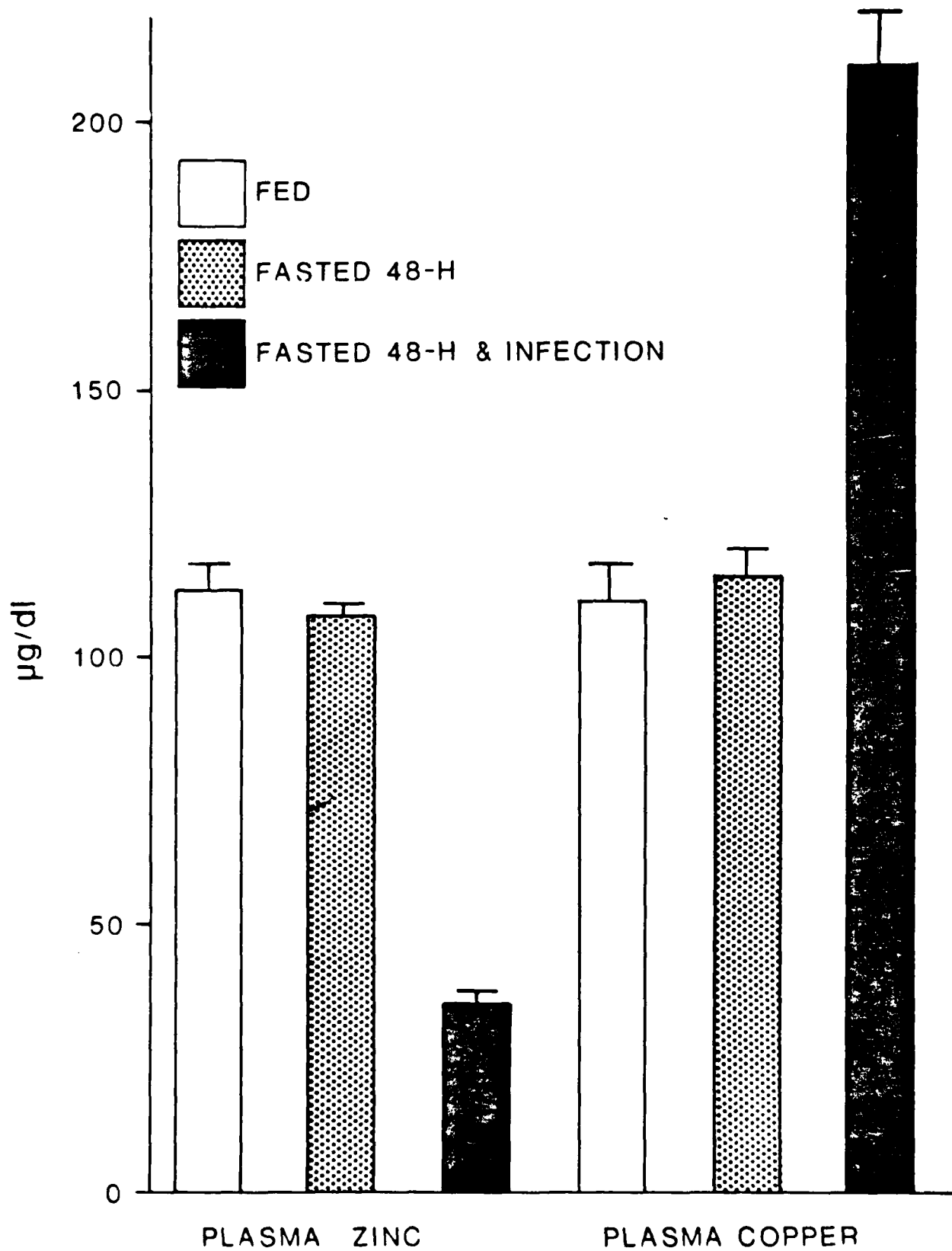
Fig. 17: Effect of thyroidectomy and adrenalectomy on ketone body

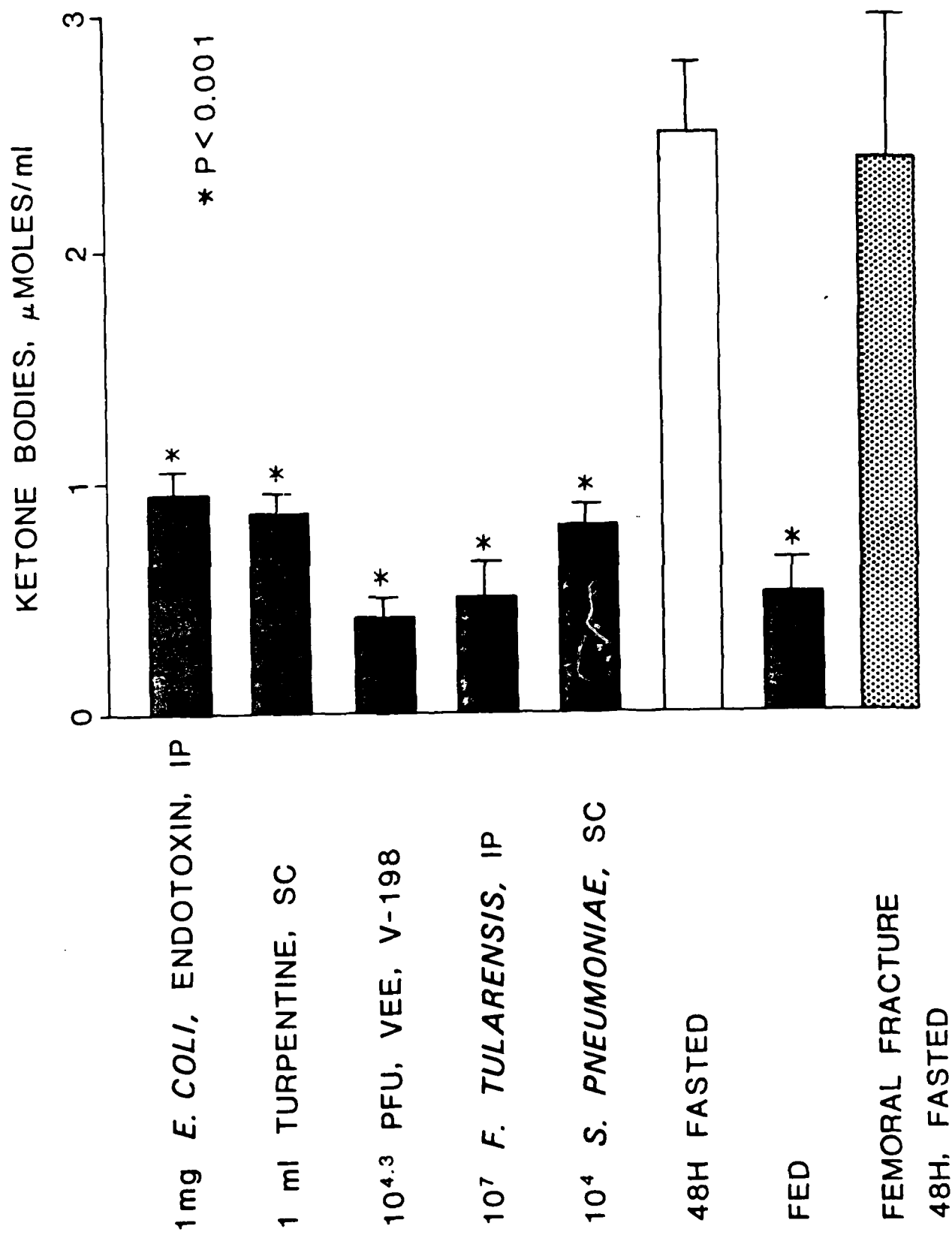
formation in the inflamed state.

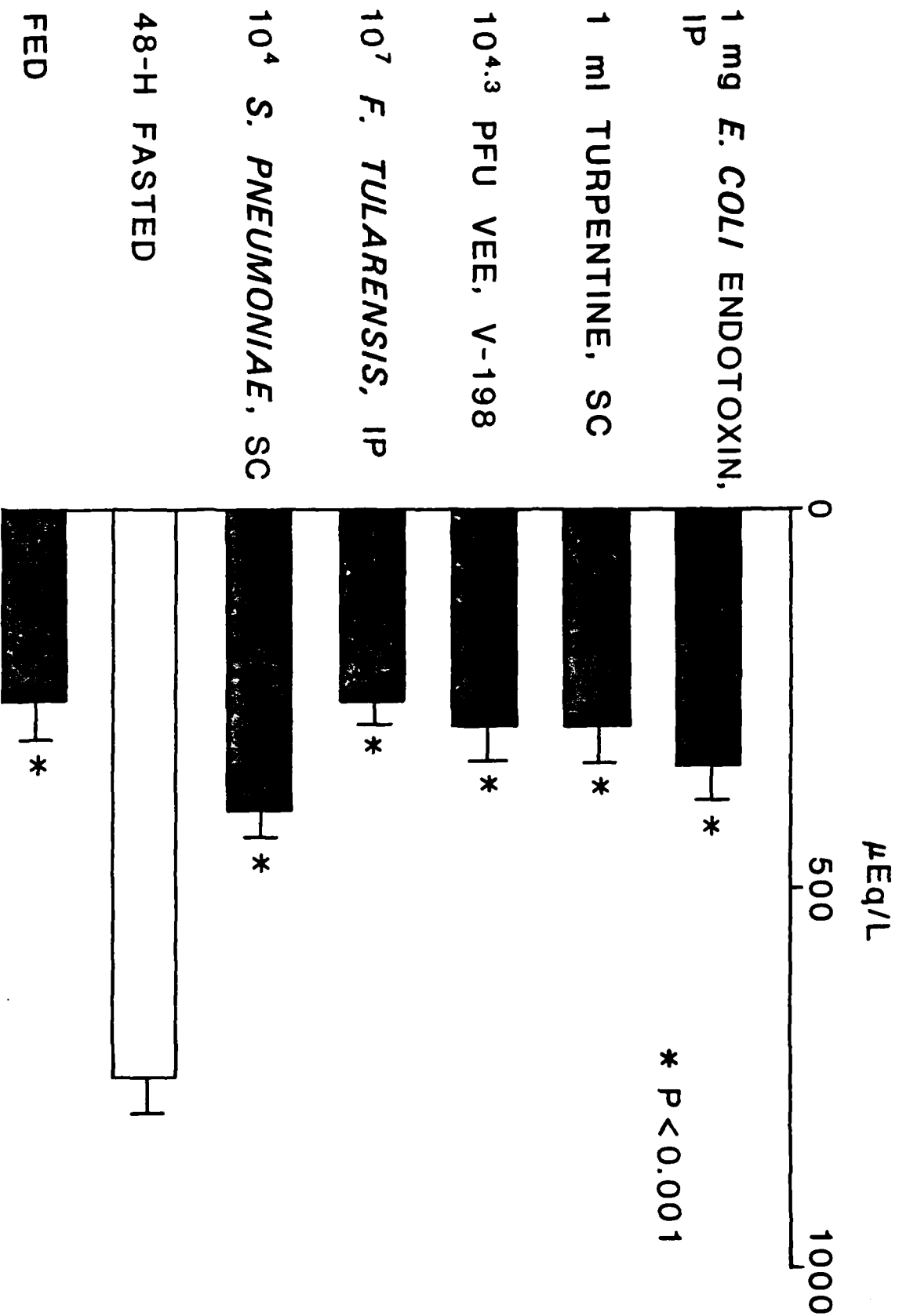
Fig. 18: Effect of infection on hypophysectomized rats and control rats on plasma ketone bodies.

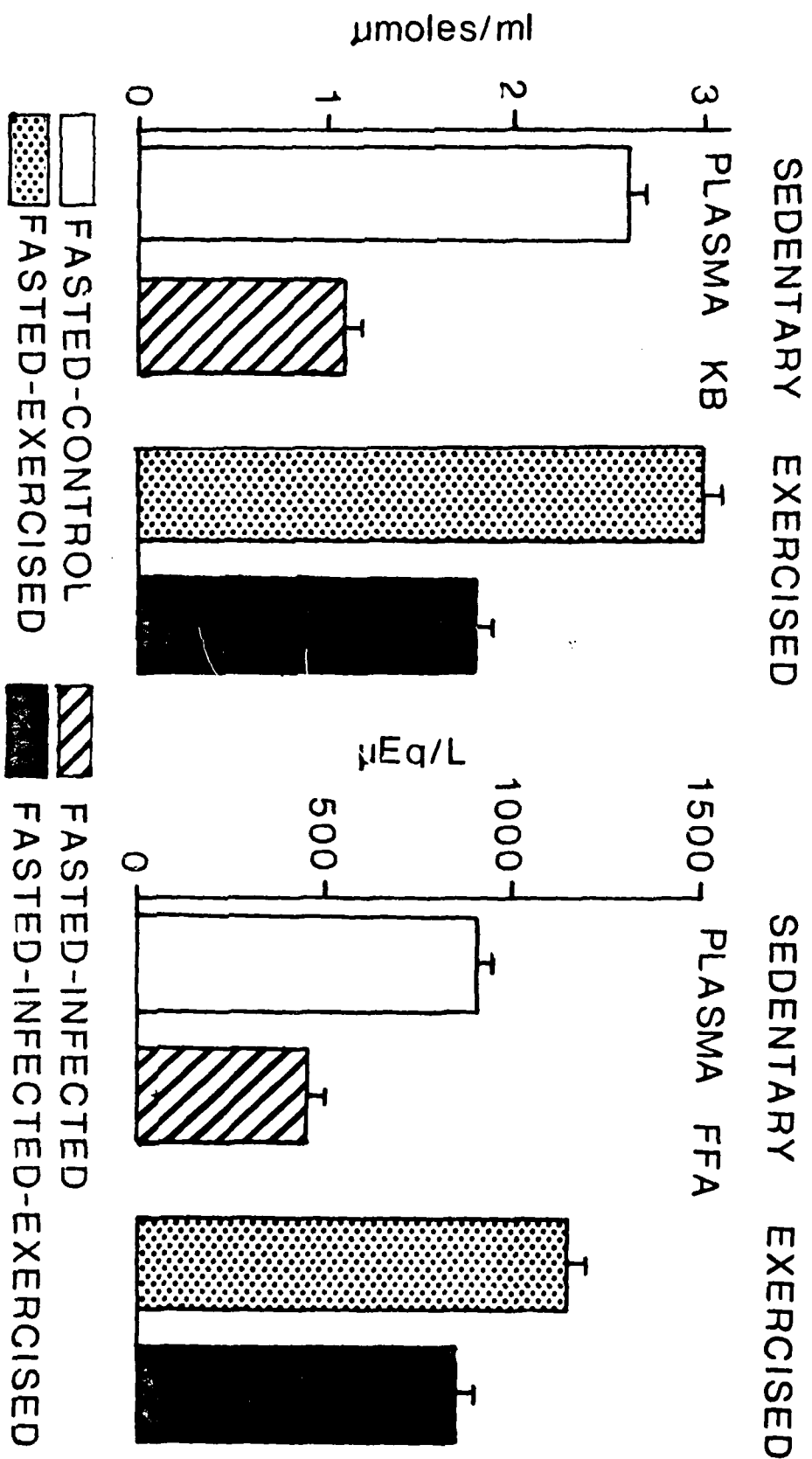
Fig. 19: Effect of infection on hypophysectomized rats and control rats on plasma free fatty acids.



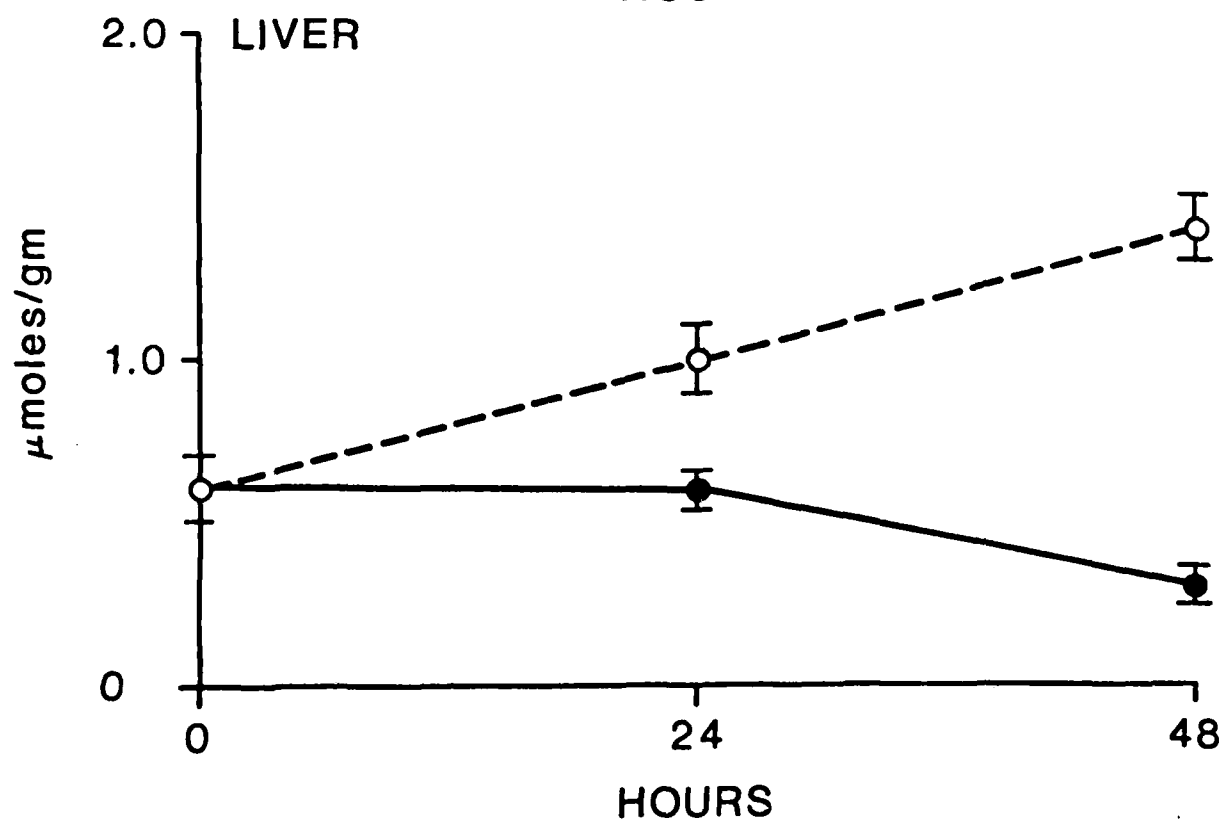
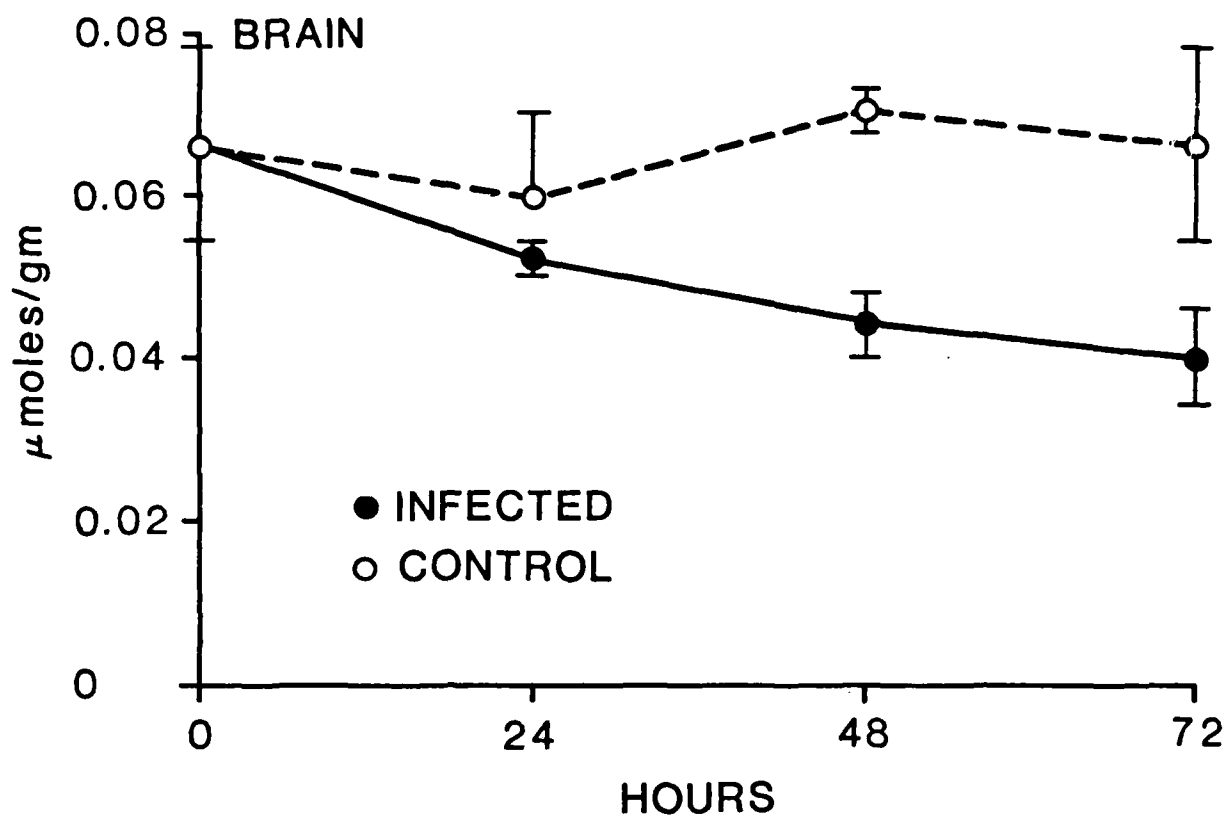


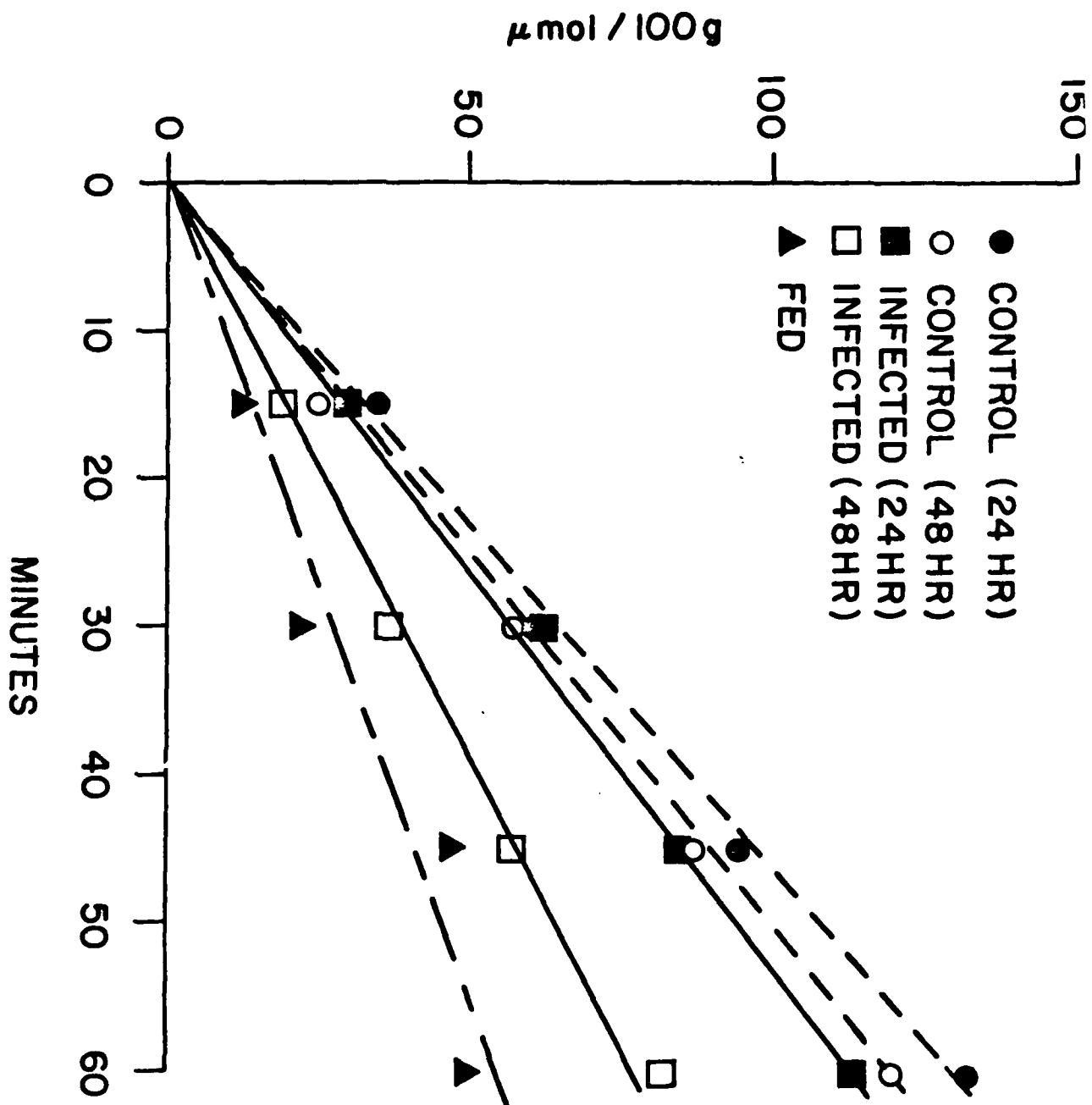


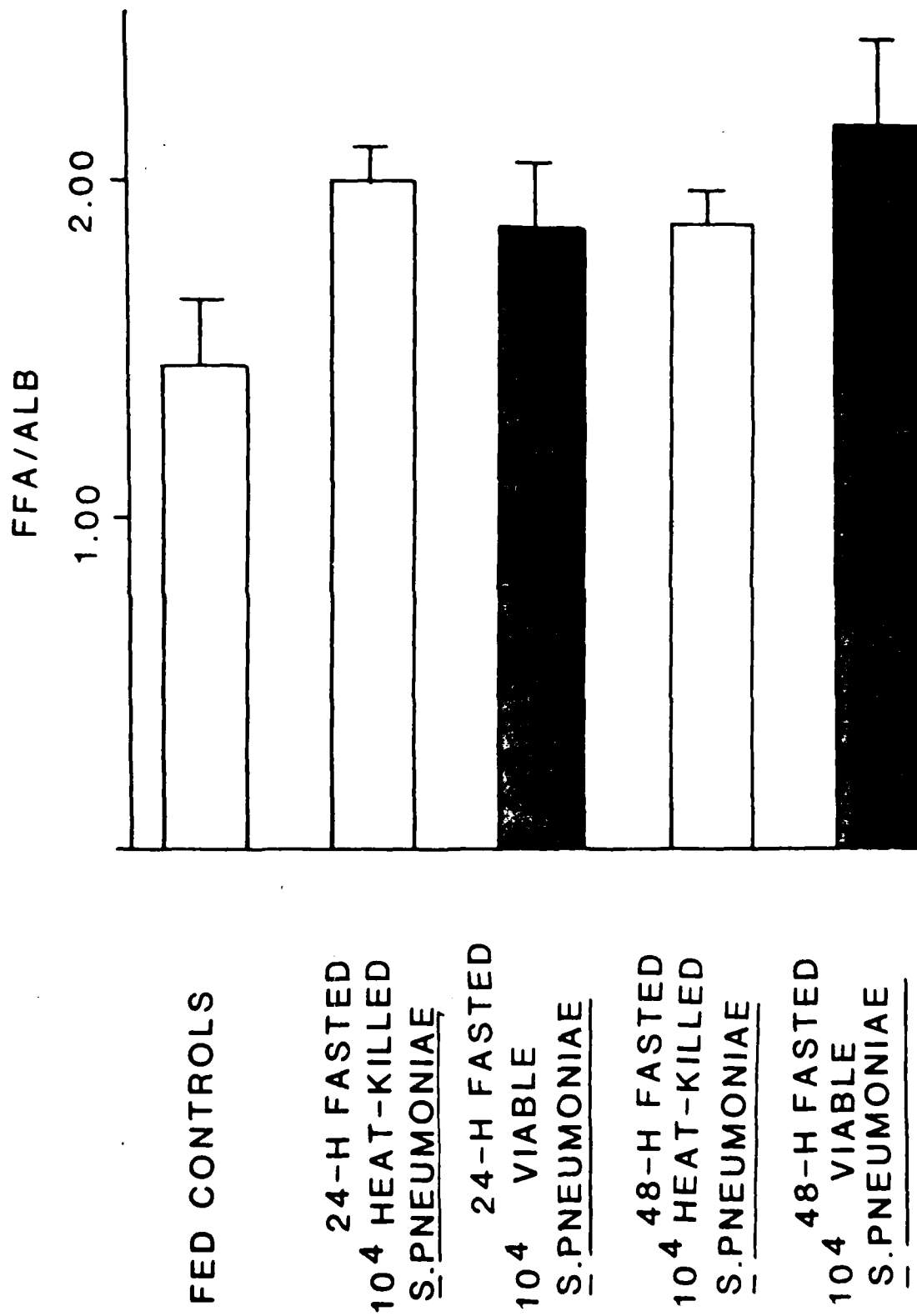


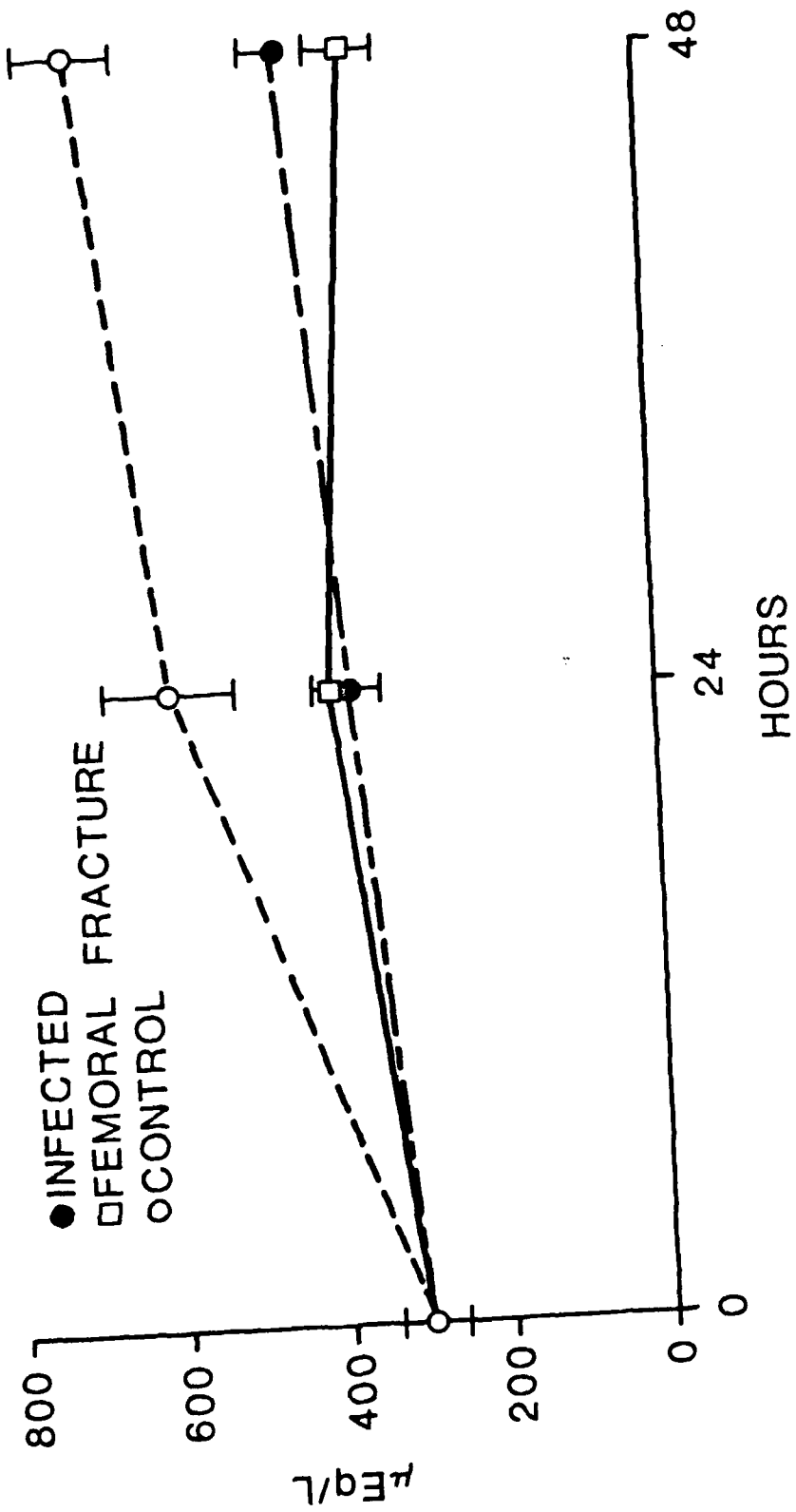


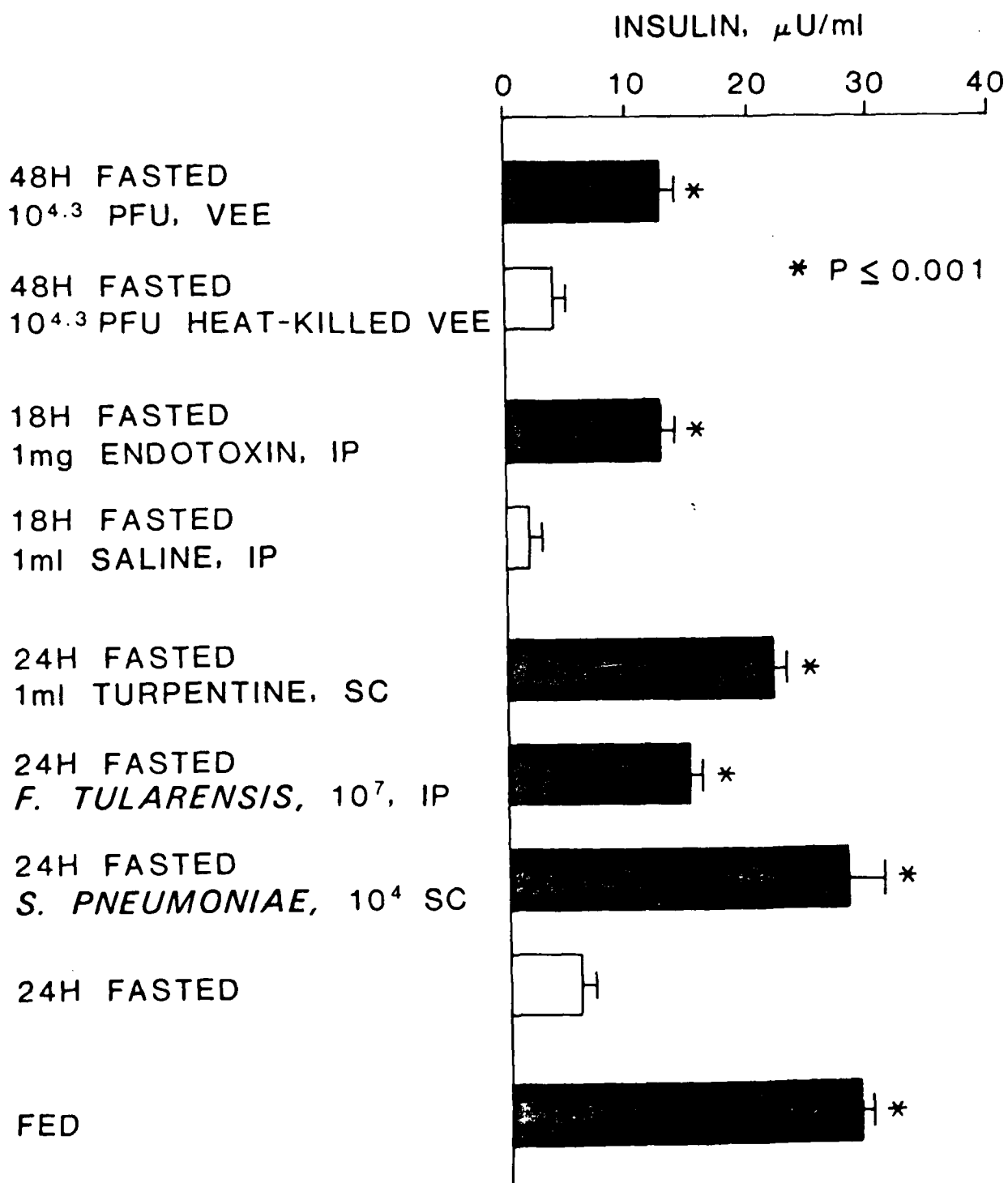
n=10 RATS/GROUP

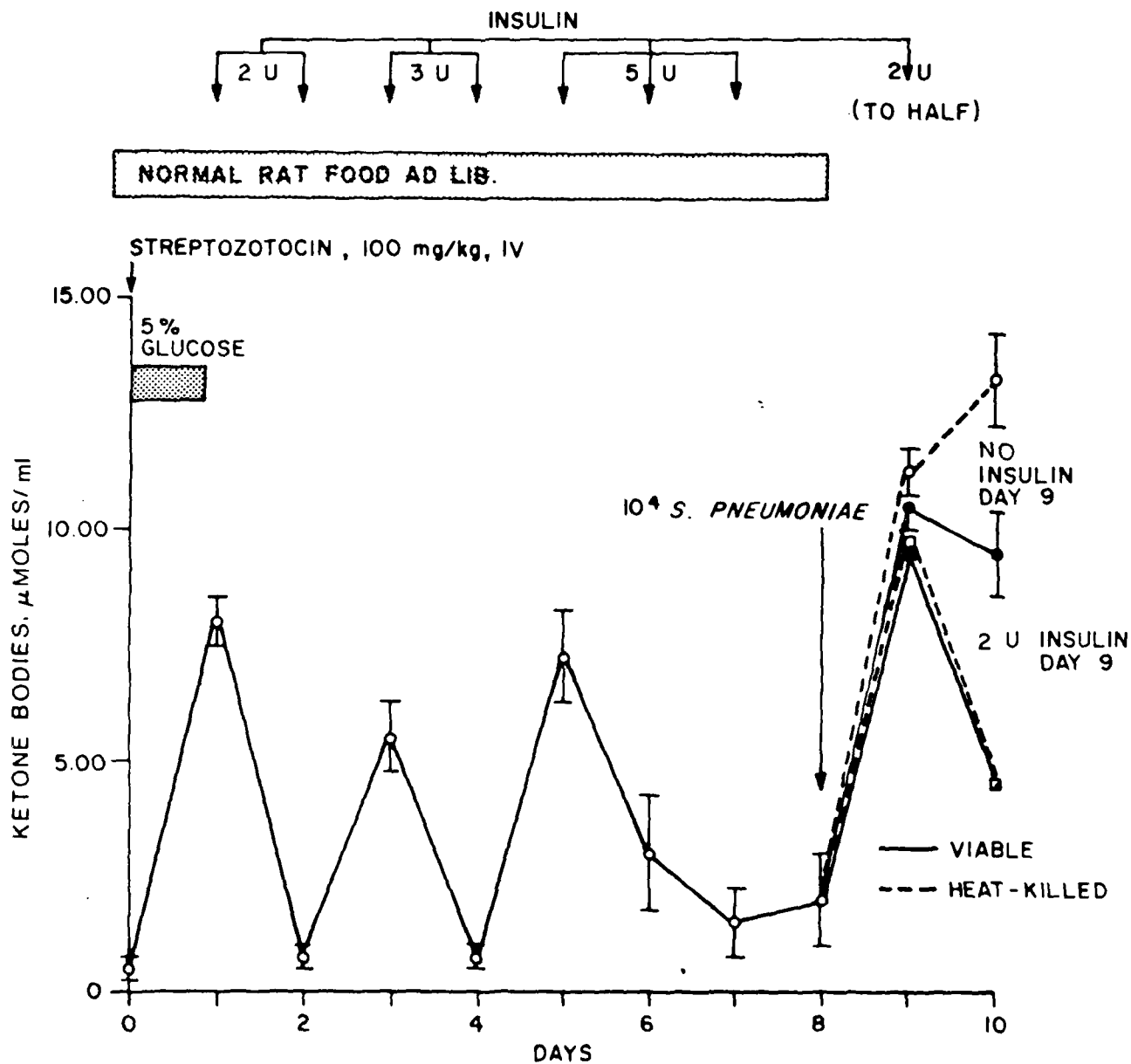


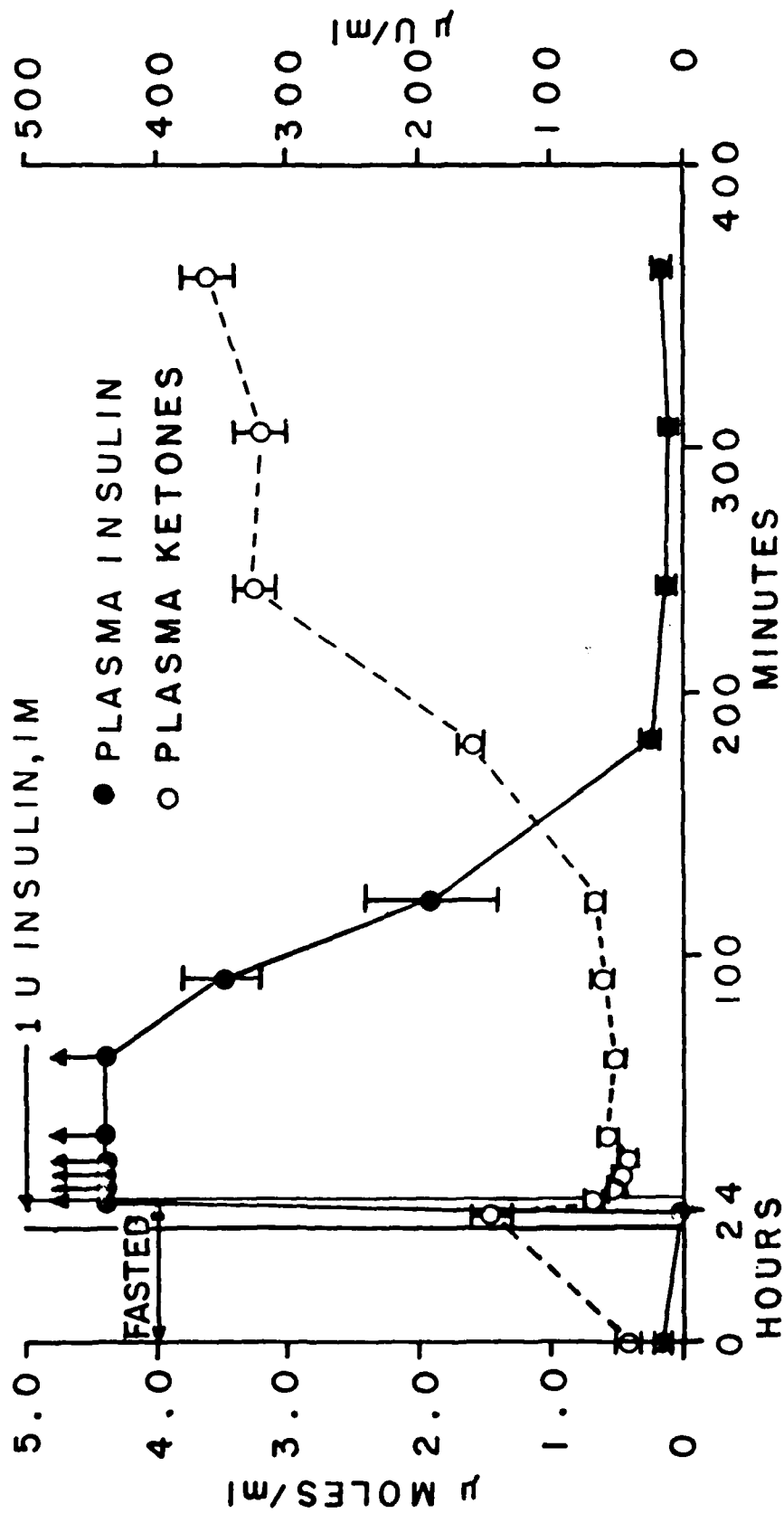


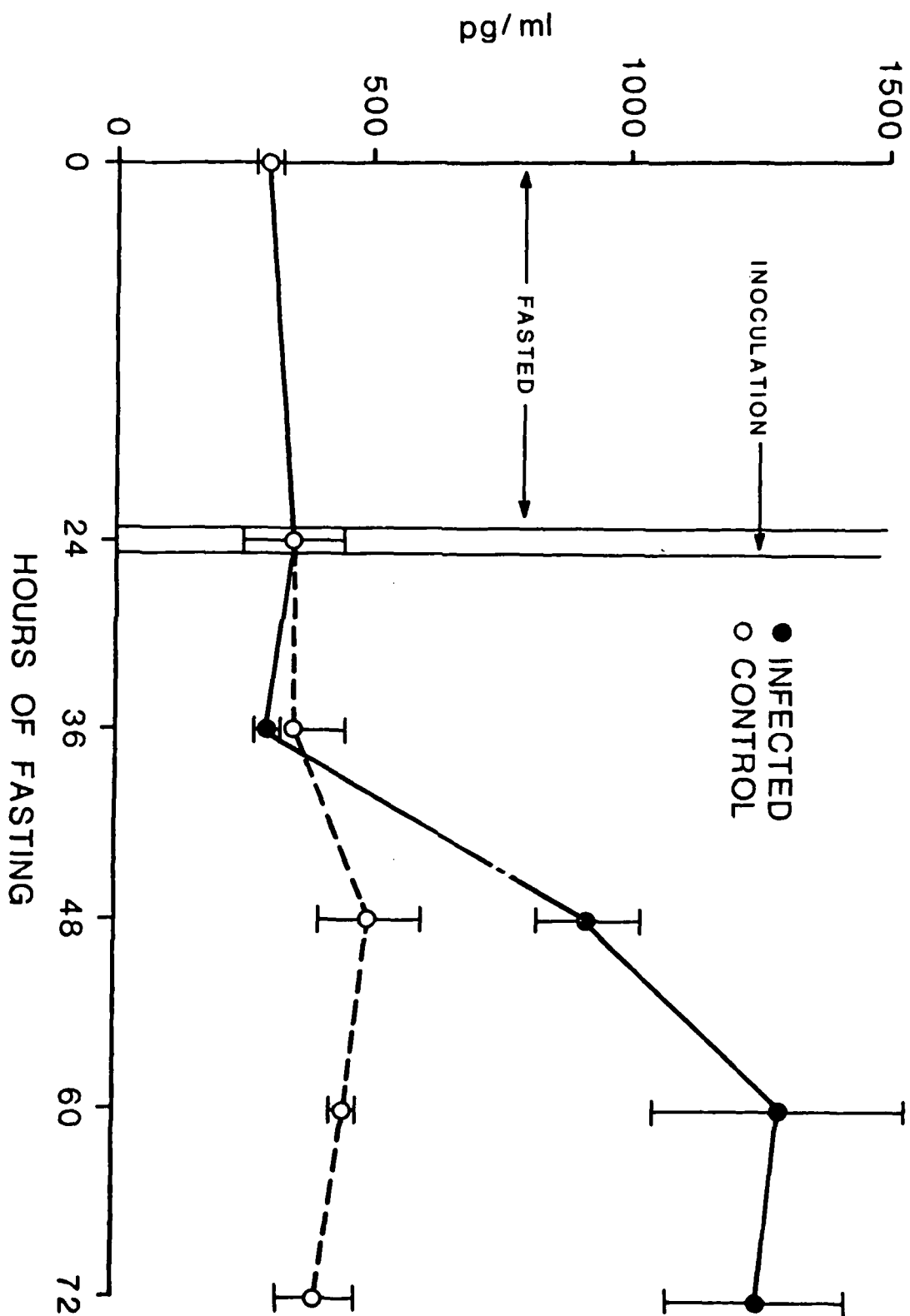


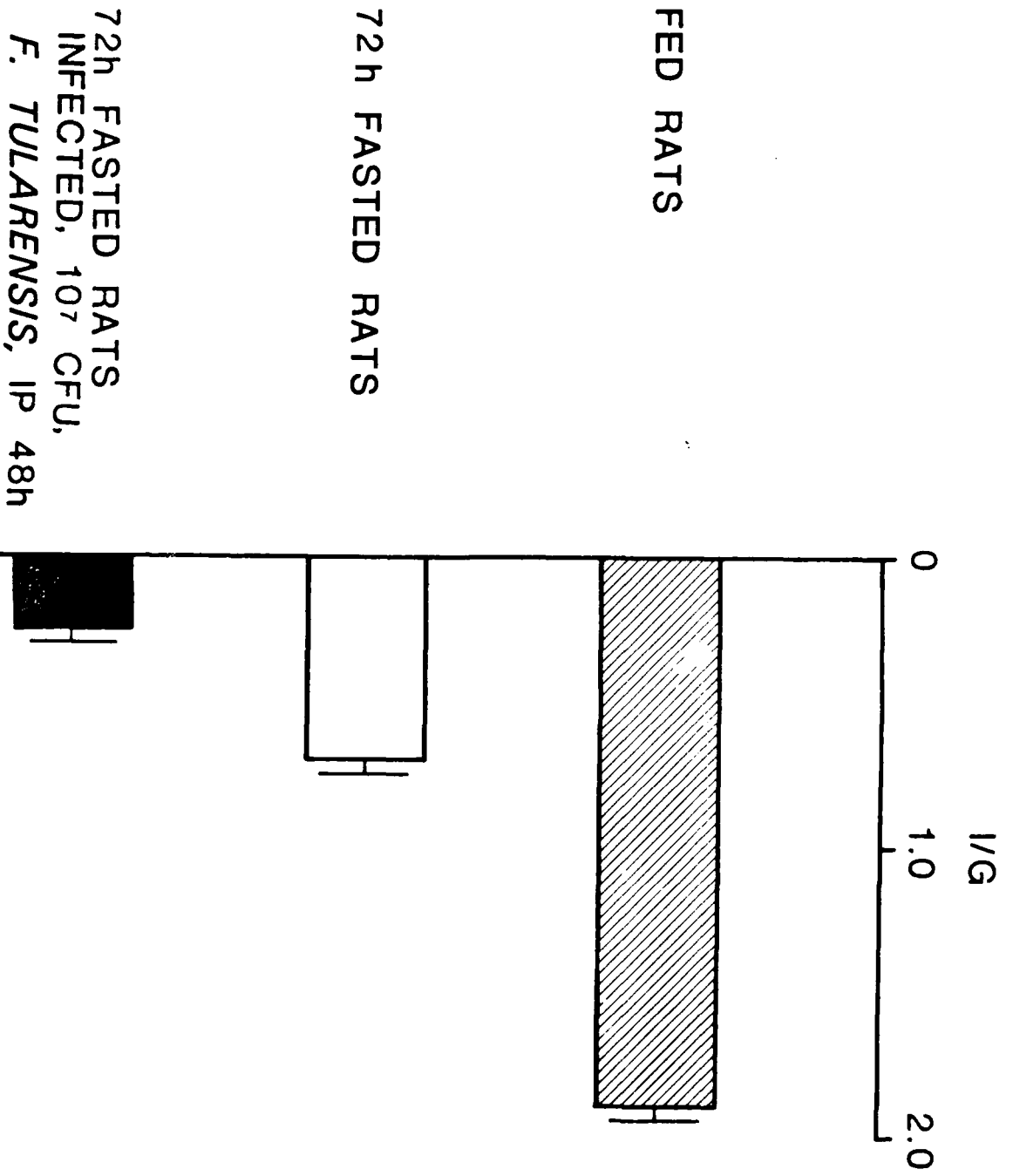








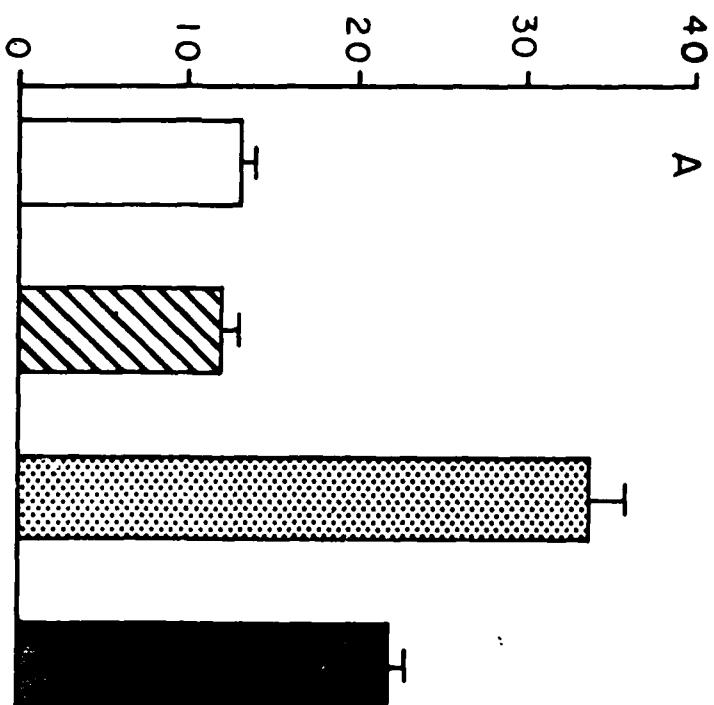




INSULIN

A

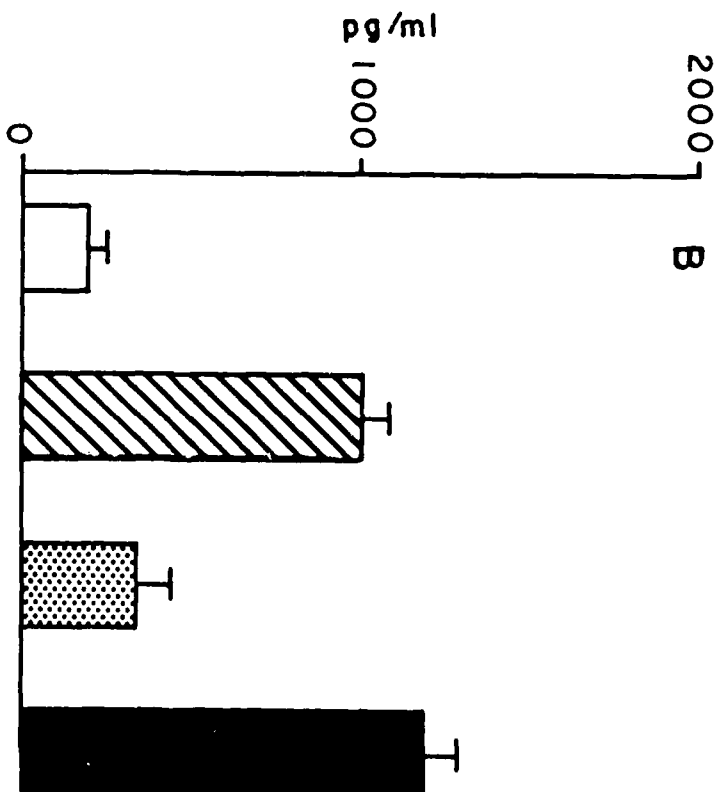
$\mu\text{U/ml}$



GLUCAGON

B

pg/ml



SEDENTARY - FASTED

EXERCISED - FASTED

SEDENTARY - FASTED - INFECTED

EXERCISED - FASTED - INFECTED

